

University of California, Los Angeles
Office for Protection of Research Subjects
HUMAN SUBJECT PROTECTION COMMITTEE (HSPC)

APPLICATION TO INVOLVE HUMAN SUBJECTS IN RESEARCH

PROJECT TITLE: Pollution-enhanced allergic inflammation & Phase II enzymes				
PRINCIPAL INVESTIGATOR:	Name Diaz-Sanchez, David	Degree(s) Ph.D.	University Title Assoc. Prof	Campus Phone No. 310 825-9261
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CO-INVESTIGATOR or FACULTY SPONSOR:	Name Casillas, Adrian	Degree(s) M.D.	University Title Adj Prof	Campus Phone No. 5-1153
	Department Medicine/CIA	Campus Mailing Address 52-175	Campus Mail Code 168017	e-mail Address acasillas@mednet.ucla.edu
PRIMARY CONTACT PERSON:	Name Eric Biederman	Campus Phone No. 68871	e-mail Address ebiederman@mednet.ucla.edu	
APPLICATION STATUS: <input checked="" type="checkbox"/> New <input type="checkbox"/> Amendment <input type="checkbox"/> Renewal Previous HSPC number, if applicable:				

INVESTIGATOR'S ASSURANCE

I certify that the information provided in this application is complete and correct.

I understand that as Principal Investigator, I have ultimate responsibility for the conduct of the study, the ethical performance of the project, the protection of the rights and welfare of human subjects, and strict adherence to any stipulations imposed by the HSPC.

I agree to comply with all UCLA policies and procedures, as well as with all applicable federal, State, and local laws regarding the protection of human subjects in research, including, but not limited to, the following:

- performing the project by qualified personnel according to the approved protocol,
- implementing no changes in the approved protocol or consent form without prior HSPC approval (except in an emergency, if necessary to safeguard the well-being of human subjects),
- obtaining the legally effective informed consent from human subjects or their legally responsible representative, and using only the currently approved, stamped consent form with human subjects,
- promptly reporting significant or untoward adverse effects to the HSPC in writing within 5 working days of occurrence,
- if I will be unavailable to direct this research personally, as when on sabbatical leave or vacation, I will arrange for a co-investigator to assume direct responsibility in my absence. Either this person is named as a co-investigator in this application, or I will advise HSPC by letter, in advance of such arrangements.

(b) (6)

8/8/04
Date

FACULTY SPONSOR'S ASSURANCE

By my signature as sponsor on this research application, I certify that the student or guest investigator is knowledgeable about the regulations and policies governing research with human subjects and has sufficient training and experience to conduct this particular study in accord with the approved protocol. In addition,

- I agree to meet with the investigator on a regular basis to monitor study progress.
- Should problems arise during the course of the study, I agree to be available, personally, to supervise the investigator in solving them.
- I assure that the investigator will promptly report significant or untoward adverse effects to the HSPC in writing within 5 working days of occurrence.
- If I will be unavailable, as when on sabbatical leave or vacation, I will arrange for an alternate faculty sponsor to assume responsibility during my absence, and I will advise the HSPC by letter of such arrangements.

Faculty Sponsor * (if PI is a student or a fellow) _____ Date _____

SECTION II - FUNDING**THIS SECTION MUST BE COMPLETED**

1. Check all of the appropriate boxes for funding sources for this research, include pending funding source(s):

☒ Extramural* ☐ UCLA Academic Senate ☐ Department ☐ Gift ☐ Other: _____

* P.I. of Contract or Grant: Diaz-Sanchez, David

Funding Source: NIH/NIAID/EPA

Contract or Grant No.: ES-03-004

Contract or Grant Title: Children's Environmental Health Center: Pollution-Enhance Allergic Inflammation and Phase II enzymes

2. If using an IDENTICAL protocol for more than one extramural funding proposal, list all funding sources below. Attach an additional sheet if more space is needed.

a. P.I. of Contract or Grant:

Funding Source:

Contract or Grant No.:

Contract or Grant Title:

b. P.I. of Contract or Grant:

Funding Source:

Contract or Grant No.:

Contract or Grant Title:

3. **STATEMENT OF FINANCIAL INTERESTS:** If you are required to submit either a Form 730-U* or a Form 740-U* to the Office of Sponsored Research, please attach a copy of those form(s) with this application. See #9 of the Guidelines for additional information regarding this requirement.

* Form 730-U, "Principal Investigator's Statement of Economic Interests" for non-governmental funded projects

* Form 740-U, "Investigator's Statement of Financial Interests" for NSF or PHS funded projects

4. Is this application for the administrative approval for a training grant, a program project, a multiple project grant, or a center grants? ☐ Yes ☒ No If yes, see Guidelines: #14.

If this application is applying for an administrative approval for funding purposes only and does not involve the participation of human subjects, do not complete the rest of this application.

SECTION III - SUMMARY INFORMATION**THIS SECTION MUST BE COMPLETED**

The review of research involving human subjects is conducted by either the Medical Human Subject Protection Committee (MHSPC) or the General Campus Human Subject Protection Committee (GCHSPC) depending on the nature of the protocol. The MHSPC is composed of primarily medical specialists, and the GCHSPC has principally socio-behavioral experts and some medical professionals. To aid the OPRS staff in evaluating which HSPC is most likely appropriate for the review of your protocol, please check all appropriate boxes in this section.

1. Will you perform medical procedures as part of this research proposal? ☒ Yes ☐ No

2. **SUBJECT POPULATION:** (Check all appropriate boxes.)

- | | |
|--|---|
| <input checked="" type="checkbox"/> Children (see Manual Chapters 4, 6, 8, & 10) | <input type="checkbox"/> Cognitively or psychologically impaired (see Manual Chapter 4) |
| <input type="checkbox"/> Elderly (see Manual Chapters 4 & 10) | <input type="checkbox"/> Institutional residents (see Manual Chapters 4 & 8) |
| <input type="checkbox"/> Fetuses (see Manual Chapter 8) | <input type="checkbox"/> Human in vitro fertilization (see Manual Chapter 8) |
| <input type="checkbox"/> Pregnant women (see Manual Chapter 8) | <input type="checkbox"/> Exclusion of minorities (see Manual Chapter 8) |
| <input type="checkbox"/> Terminally ill (see Manual Chapter 8) | <input type="checkbox"/> Prisoners or parolees (see Manual Chapter 8) |
| <input type="checkbox"/> Comatose (see Manual Chapter 4) | <input type="checkbox"/> Non-English speaking (see Guidelines #11 & Manual Chapter 8) |
| <input type="checkbox"/> Cancer patients (see Guidelines #4) | <input checked="" type="checkbox"/> UCLA students/staff (see Guidelines #10 & Manual Chapter 8) |

3. If the research involves any of the following, check the appropriate boxes:

- | | |
|--|--|
| <input type="checkbox"/> Interviews | <input type="checkbox"/> HIV/AIDS |
| <input type="checkbox"/> Survey/questionnaire | <input checked="" type="checkbox"/> Clinical studies |
| <input type="checkbox"/> Behavioral observation | <input type="checkbox"/> Investigational drugs (if checked, complete Section I) |
| <input type="checkbox"/> Deception | <input type="checkbox"/> Investigational devices (if checked, complete Section II) |
| <input type="checkbox"/> Waiver of consent | <input type="checkbox"/> Radiation (see Guidelines #5) |
| <input type="checkbox"/> Study of existing data (see Guidelines #12) | <input type="checkbox"/> Controlled substances (see Guidelines #6) |
| <input checked="" type="checkbox"/> Study of human biological specimens (see Guidelines #12) | <input type="checkbox"/> Microorganisms or recombinant DNA (see Guidelines #7) |
| <input type="checkbox"/> Venipuncture (≤ 450 cc) | <input type="checkbox"/> Potential development of commercial product from human biological materials (see Guidelines #8) |
| <input type="checkbox"/> Genetic research | <input type="checkbox"/> PI or Co-PI is the treating physician |

4. **LOCATION(S) OF RESEARCH TO BE CONDUCTED AT:**

- | | |
|--|---|
| <input checked="" type="checkbox"/> UCLA campus | <input type="checkbox"/> Santa Monica-UCLA Medical Center |
| <input type="checkbox"/> Other locations, specify: _____ | |

5. **LAY LANGUAGE SUMMARY:** (Please use non-technical language that is understood by nonscientific members to summarize the proposed research project. The information must include: (1) a brief statement of the problem and related theory supporting the intent of the study, and (2) a brief but specific description of the procedure(s) involving the human subjects. Attach an additional page as necessary. However, please do not exceed one single-spaced, type-written page.)

See attached

SECTION IV - PROTOCOL SUMMARY**THIS SECTION MUST BE COMPLETED**

INSTRUCTIONS: In order to review your proposal, the Human Subject Protection Committee (MHSPC) must have all of the following information. Each topic must be titled using the boldface subheadings listed below. State "Not Applicable" for topics that are not applicable to your application. Address each topic independently in the sequence listed without reliance on information covered under other subparts. Attaching sections of the grant application is not an acceptable substitute. Provide sufficient information for effective review by all members of the HSPC, including non-specialists. Define all abbreviations and terms not part of common language and use simple words and sentence structure as much as possible. Unless justification is provided, Section IV of this application must not exceed 10 pages (excluding references). Number each page, beginning with page one for the first page of Section IV.

INFORMATION REGARDING RENEWAL APPLICATION (1)

1. **Renewal Application:** What benefits to the participating subjects or to the society have been derived? Please also provide a summary of the research activities during the previous approval periods regarding the following issues:
 - a) How many subjects have been enrolled since the date of last approval and since the initial approval?
 - b) Has there been any difficulty obtaining/retaining subjects or obtaining informed consent during the previous approval period? If yes, describe:
 - Approximately how many potential subjects have refused participation?
 - How many subjects have voluntarily withdrawn participation at their own request?
 - How many subjects have withdrawn participation at the request of the PI?
 - c) Have there been any unexpected reactions or complications since last scheduled annual review? If yes, please attach Adverse Event Reports (Form HS-5). If you have submitted the Adverse Event Reports, please state so.
 - d) Approximately how many more subjects are required to complete the study?

PURPOSE OF THE STUDY, THE BACKGROUND AND THE LITERATURE REVIEW (2-3)

2. **Purpose of the Study:** What are the specific scientific objectives (aims) of the research?
3. **Background:** State the background of the study. Include a critical evaluation of existing knowledge, and specifically identify the information gaps which the project is intended to fill. Describe previous work in animal and/or human studies that provide a basis for the proposed research and that support the expectation of obtaining useful results without undue risk to human subjects.

Note: Include appropriate citations to the scientific literature or attach a copy of literature review.

CHARACTERISTICS OF THE SUBJECT POPULATION (4-6)

4. **Number of Subjects:** What is the anticipated number of subjects to be enrolled at UCLA and, in the case of multi-center research, the total number of subjects for the entire project?
5. **Inclusion/Exclusion Criteria:**
 - a) What are the criteria for inclusion and exclusion?
 - b) How will eligibility be determined, and by whom?
 - c) Are any inclusion or exclusion criteria based on age, gender, pregnancy or childbearing potential, or racial/ethnic origin? If so, explain and justify.

Note: Equitable inclusion of both men and women of all ages, and individuals from diverse racial/ethnic backgrounds, is important to assure that they receive an equal share of the benefits of research and that they do not bear a disproportionate share of its burdens. Participation of adult subjects of both genders and diverse racial/ethnic backgrounds should not be restricted without medical or scientific justification.

6. **Vulnerable Subjects:** Will any vulnerable subjects be included? If so, identify the subject groups and justify their involvement.

Examples of vulnerable subjects: children, elderly, pregnant women, fetuses, cognitively impaired individuals, persons with severe psychological disorders, terminally ill patients, emergency patients, institutional residents, prisoners, parolees, non-English speaking subjects, and UCLA students/staff.

SUBJECT IDENTIFICATION AND RECRUITMENT (7)

7. **Method of Subject Identification and Recruitment:** What method(s) will be used to identify and recruit prospective subjects? Attach a copy of any planned advertisements/notices and letters to potential subjects.

Note: The identification and recruitment of subjects must be ethically and legally acceptable and free of coercion. Procedures used to recruit subjects should be designed to reach diverse populations. Vulnerable subjects, such as persons in nursing homes or institutions, should not be recruited merely for the sake of convenience.

METHODS AND PROCEDURES (8-11)

8. **Methods and Procedures Applied to Human Subjects:** Describe the study design and all procedures (sequentially) to which human participants will be subjected. Identify all procedures that are considered experimental and/or procedures performed exclusively for research purposes.

Note: A clinical research protocol may involve interventions that are strictly experimental or it may involve some aspect of research (e.g., randomization among standard treatments for collection and analysis of routine clinical data for research purposes). It is important for this section to distinguish between interventions that are experimental and/or carried out for research purposes versus those procedures that are considered standard therapy. In addition, routine procedures performed solely for research purposes (e.g., additional diagnostic/follow-up tests) should be identified.

9. **For Research Involving Survey, Questionnaires, etc.:** Describe the setting and mode of administering the instrument (e.g., by telephone, one-on-one, or group) and the provisions for maintaining privacy and confidentiality. Include the duration, intervals of administration, and overall length of participation.

Note: If the protocol for the interviews or the questionnaires are not yet designed, provide a sample of the questions or describe the subject matter to be covered. (If the instrument has been prepared even in draft form, submit a copy.) The final survey instruments or questionnaires must be reviewed and approved by the HSPC before they may be used.

10. **FDA Approval:** Are there any investigational drugs or biological agents used in this study? If yes, please complete Section IV. Are there any investigational devices used in this study? If yes, please complete Section V. If the study does not involve any investigational drugs or devices, this should be stated.

11. **Data Collection, Storage and Confidentiality:**

- a) How will data be collected and recorded? Will it be associated with personal identifiers or coded to protect personal privacy?
- b) Where will the data be stored during the study and how will it be secured?

- c) Who will have access to the data and/or to the codes? If data with subject identifiers will be released, specify the person(s) or agency to whom this information will be released.
- d) What will happen to the data when the research has been completed?

Note: The principal investigator is responsible for taking all necessary steps to maintain confidentiality of data. This includes coding data and choosing an appropriate and secure data storage mechanism that will prevent unauthorized access to the data. Where appropriate, the principal investigator should seek a certificate of confidentiality from the federal government.

RISK/BENEFIT ASSESSMENT (12-17)

12. **Potential Risks and Discomforts:** What are the potential risks/discomforts associated with each intervention or research procedure? If data are available, estimate (a) the probability that a given harm may occur, (b) its severity, and (c) its potential reversibility.

Note: A risk/discomfort is a potential harm associated with the research that a reasonable person would consider important in deciding whether to participate in the research. Risks can be generally categorized as physical, psychological, sociological, economic and legal.

13. **Risk Classification:** What is the overall risk classification of the research: minimal, greater than minimal, significant, or unknown?

Note: According to HHS/FDA Regulations minimal risk means "The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." When the risks associated with a new procedure or product are unknown, they cannot be classified as "minimal." Your estimation of risk determines the Emergency Care and Compensation for research-related injury clause in the informed consent form.

14. **Minimizing Risks:** What procedure(s) will be utilized to prevent/minimize any potential risks or discomfort?

Note: All potential risks and discomfort must be minimized to the greatest extent possible by using procedures such as appropriate monitoring and withdrawal of the subject upon evidence of a specific adverse event or clinical sign(s). This section should reflect that all appropriate steps will be taken to protect subjects from harm.

15. **Potential Benefits:**

- a) What potential benefits may subjects receive as a result of their participation in the research?
- b) What potential benefits to society may be expected from this research?

Note: Societal benefits generally refer to the advancement of medical knowledge and/or possible benefit to future patients

16. **Therapeutic Alternatives:** What therapeutic alternatives are reasonably available in the non-research and/or research context that may be of benefit to the potential subjects?

Note: This section should include a reasonably detailed description of the therapeutic alternatives that could be used to treat the patient should they elect not to participate in the protocol.

17. **Risk/Benefit Ratio:** What is the risk/benefit ratio of the research, compared with that of the available alternatives?

Note: The potential benefits of research must justify the risks to human subjects. Some risks may not be reasonable, no matter how important the potential benefits. The risk/benefit ratio of the research must be at

least as favorable for the subjects as that presented by standard treatments for their condition. When comparing the risk/benefit ratio of research with that of available alternatives, the alternative of doing nothing, or "watchful waiting," should be included in the analysis.

FINANCIAL CONSIDERATIONS (18-20)

18. **Payment for Participation:** Describe all plans to pay subjects, in cash or in kind. If no payment is planned, that should be stated. Information regarding payment consideration should include: Will subjects receive any financial inducement or payment for participation? Will they receive services or other benefits instead of cash? Will they be reimbursed for travel and other expenses? What conditions must be fulfilled by subjects to receive either full or partial payment?

Note: The FDA encourages a prorated system of payment whereby subjects who do not finish the protocol are paid in proportion to the part completed. The amount of payment must be justified and not constitute undue inducement of the subject to participate in the research. If a non-prorated system of payment will be used, this should be justified in this section.

19. **Financial Obligations of the Subjects:** What financial obligations will subjects incur as a result of participating in the study? Will subjects have to pay for any of the treatment(s) they receive or tests performed in the research?

Note: This section should clarify who will pay for procedures associated with the study as well as financial responsibility for routine clinical care (e.g., Diagnostic tests, hospitalization, follow-up). Insurance and other third party payers may not cover procedures associated with participation in research (even if they might have paid for some of the procedures in connection with standard therapy). Consequently, subjects' costs may be increased as a result of additional follow-up examinations and/or tests required by the research.

20. **Emergency Care and Compensation for Research-Related Injury:** If the research presents greater than minimal risk, what emergency care is available in case of research-related injury? Who will be responsible for the cost of such care? Will subjects be compensated for out-of-pocket expenses or lost wages if they suffer a research-related injury?

Note: Standard language for explaining this to prospective subjects is provided in the instructions for preparing the Consent Form. (Forms HS-2 & HS-3).

INFORMED CONSENT (21-26)

21. **Capacity to Consent:** Will all adult subjects have the capacity to give informed consent? If not, describe the likely range of impairment and explain how, and by whom, their capacity to consent will be determined.

Note: In research involving more than minimal risk, capacity to consent should be determined by a psychiatrist, clinical psychologist, or other qualified professional not otherwise involved in the research. Individuals who lack the capacity to consent may participate in research only if consent is given on their behalf by a legally authorized representative.

22. **Personnel Inviting Participants:** Who will be inviting subjects to participate and what will they say? Identify by name and training the individual(s) authorized to describe the research to subjects/representatives and to invite their participation.

Note: Only those individuals authorized to solicit consent may sign the consent form confirming that the prospective subject was provided the necessary information and that any questions asked were answered.

23. **Process of Consent:** How and where will the consent process take place? How will it be structured to enhance independent and thoughtful decision-making? What steps will be taken to avoid coercion or undue influence?

Note: Consider: a) the environment and location where informed consent will be solicited; b) the timing of the process (e.g., in relation to hospital admission, surgery, medication, stressful events); c) the involvement of someone other than the investigators to help explain the research; and d) opportunity for the prospective subjects/representatives to discuss participation in the research with family, friends, or their advisors before signing the consent form.

24. **Comprehension of the Information Provided:** How—and by whom—will it be determined whether the subjects or their legally authorized representatives understand the information provided?

Note: This section should clearly document that the investigator has an adequate plan in place to assure existence of an acceptable level of comprehension before consent is documented. The principal investigator (or approved designee) is responsible for assuring that prospective subjects or their representatives have sufficient understanding of the research to make an informed decision about participation. It is important that they understand the purpose of the research, the nature and duration of the procedures, any risks and discomforts involved, the possible benefits to the subjects and others, and their right to withdraw consent at any time without penalty. Willingness to sign the consent form is not an adequate demonstration of their understanding. Some investigators try to determine the level of prospective subjects' comprehension by questioning them about the research. (This approach is useful with children and adolescents, as well as with adults of uncertain capacity to consent.)

25. **Information Withheld From Subjects:** Will any information about the research purpose and design be withheld from potential or participating subjects? If so, explain and justify the non-disclosure and describe plans for post-study debriefing.

Note: Any non-disclosure must be approved by the HSPC and may not exclude information that a reasonable person would want to know in deciding whether to participate in the research. In addition, the alteration in the consent procedure must be approvable under 45 CFR 46.116(d): (1) the research involves no more than minimal risk to the subjects; (2) the waiver or alteration will not adversely affect the rights and welfare of the subjects; (3) the research could not practicably be carried out without the waiver or alteration; and (4) whenever appropriate, the subjects will be provided with additional pertinent information after participation.

26. **Consent/Assent Forms:** Specify the form(s) that will be used among the following: adult consent form, parental consent form, proxy consent form, youth assent form (age 13-18), and/or child assent form (age 7-12).

Section III - Summary Information

5. LAY LANGUAGE SUMMARY: :

1) Background: Allergy and asthma have been increasing since the onset of the industrial revolution. In particular the last 30 years have seen a dramatic rise in the incidence of hayfever and asthma. While this may be attributable to many reasons, many studies point to pollution as a risk factor. Changes in the quality of the air we breath related to air borne "pollutants" are likely one critical factor in the increasing worldwide incidence, prevalence, and severity of allergic airway disease. Previous work by others and us show that diesel exhaust particles can increase allergy symptoms and immunological changes. In vitro and animal studies suggest that natural chemicals (antioxidants) may protect against allergic reactions. We now know that the effect that pollutants have on people is dictated by the levels of these natural chemicals. We know that pollutants have increased effects on children. We therefore want to test whether the reason for this is that children produce less of these chemicals than adults. We will do this by performing a procedure we have done on hundreds of adults over many years, a nasal challenge with the model pollutant: diesel exhaust particles (DEP) in combination with nasal lavage. These procedures involve minimal risk. We will then measure the amount of antioxidants produced upon challenge. We are now requesting permission to perform these procedures on children aged 10-15 years and compare their responses to adults aged 21 and over.

2) Procedures:

Nasal Lavage: nasal lavage simply consists of having the individual put 5cc of salt water in each side of the nose. This is done with the tongue up against the back of the throat so the fluid does not get swallowed. The fluid is left in place for about 30 seconds, the head is then tilted forward and the fluid is allowed to drain into a basin

Diesel exhaust particle challenge. A small amount of fluid (about 5 drops) containing diesel exhaust particles in an amount up to that equivalent to about 2 days exposure to Los Angeles air is simply sprayed into the nose.

Section IV -- Protocol Summary

1. Renewal Application: N/A

2. Purpose of the Study:

The goal of this study is to determine whether children are more susceptible to the effects of pollution and why. We will test the hypothesis that human antioxidant enzyme production in children is less than that seen in adults in response to pollution and that this explains their increased susceptibility to respond to the immune enhancing effects of pollution. Over the past 10 years, we have defined and refined our model of the effect of diesel exhaust particles (DEP) on human allergic airway disease and elucidated the underlying cellular and molecular mechanisms for the DEP adjuvant effect. We will use this established and safe model to test our hypothesis.

3. Background:

Allergic airway disease has become more common and severe in spite of our far greater understanding of many issues related to allergic inflammation and allergic airway disease. Changes in childhood infections, diet, home construction, air quality, and personal activity (both the amount and nature) likely all play some role. (1) We believe that combustion products, exemplified by diesel exhaust particulates (DEP) are one important factor in the changes in allergic airway observed over the last 200 years and are also likely contributors to the more recent upturn in the past several decades. We have investigated DEP as a model pollutant. DEP have a particulate and chemical component and make up an important part of the particulate material (PM) in the air column that can be quantified, analyzed and fractionated (2). Furthermore, DEP make up, as substantial part of the 10 micron or smaller particles (PM10) in a city such as Los Angeles (3).

Our previous studies have compared individuals exposed experimentally to allergen alone or to allergen plus DEP at the equivalent dose of 2 days exposure in Los Angeles. We have shown that DEP will augment allergen-induced IgE (allergic antibody) responses, histamine production, cytokine and chemokine synthesis and symptom severity. (3-5)

Several studies have suggested that generation of reactive oxygen species (ROS) are important in the pathogenesis of allergic airway disease and exposure to xenobiotics such as DEP. Following an initial report by Tagafer et al (11), extensive studies in mice by Sagai et al (6-13) have shown that both acute and chronic exposure to diesel by acute intratracheal instillation or chronic inhalation leads to increased expression of oxidative stress in the lung in association with airway hyper responsiveness. These same investigators also showed that, in vitro, DEP extracts generate oxidative stress (measured as super oxide) when mixed with a microsomal preparation of lung tissue. They went on to show that pretreatment with super oxide dismutase was able to inhibit the inflammatory effects of DEP in vivo and that glutathione and other antioxidants was able to inhibit the in vitro effect. Similarly treatments with either a nonspecific or specific inhibitor of ROS were able to protect mice against DEP induced airway inflammation. Oxidative stress induced by allergen challenge has also been shown to enhance airway hyper responsiveness in dogs and sheep (14,15). Data for the primary involvement of oxidative stress in human allergic airway diseases is less well developed. Following pulmonary allergen challenge, superoxide is generated in the human lung. We have found that within two hours following exposure to DEP there is a marked enhancement of

the generation of ROS in nasal lavage cells measured as DFP fluorescence and as a shift in the ratio of reduced to oxidized glutathione.

Overall, these results provide strong evidence for the involvement of the oxidative stress pathway *in vivo* in the observed human outcomes. Humans and other vertebrates have developed natural defenses to combat the effects of oxidative stress. These antioxidants can reduce or prevent formation of ROS. In humans genetic polymorphisms have been identified in 3 genes coding for three of the most important antioxidants (NQO1, GSTM1 and HO-1). In each case a rare polymorphism will result in the complete deficiency of the gene to be able to make the antioxidant (16-18). We have shown that individuals with these polymorphisms will be more susceptible to the allergic-enhancing effects of DEP. (19).

It is taken as a given that children are at increased risk to air pollution than adults. However, the reasons for this are unknown. The common answer is that their "systems are still developing". Research into the question of what exactly is involved is essential for us to be able to devise strategies to protect children. We believe that a key factor is that children's antioxidant responses to pollutants are different than adults. Our study therefore, proposes to address this question directly by using our established DEP-nasal challenge model and measuring Phase II expression in adults and children.

References

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3. Peterson, B. and Saxon A., Global Increases in Allergic Respiratory Disease: The Possible Role of Diesel Exhaust. *Ann. All. Asthma, Immunol*, 77:263-8, 1996.
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4. **Number of Subjects:** 40 children and 20 adults during the course of the study

5. **Inclusion/Exclusion Criteria:**

a) What are the criteria for inclusion and exclusion?

A. Inclusion criteria

Age 10 to 15 years old, or 21 years and over.

B. Exclusion criteria:

Exclusion from the study will occur if subjects have any of the following conditions:

- i) A history of lung problems (including asthma), bleeding, neuromuscular, liver, kidney or heart disorders. History of anaphylaxis. Recent upper respiratory infection (less than 4 weeks prior to study) or other active infection.
- ii) Active smoker or smoker in past 2 years.
- iii) Treatment with topical steroids (<3 months), systemic steroids (<3 months) oral antihistamines (<1 month) or ever having been on allergy immunotherapy.

b) How will eligibility be determined, and by whom?

Eligibility will be determined by asking the subjects if they wish to participate or not. The subject and the P.I. and in the case of children, the parents, will determine eligibility.

c) Are any inclusion or exclusion criteria based on age, gender, pregnancy or childbearing potential, or racial/ethnic origin? If so, explain and justify.

There is no exclusion except for age. Subjects must be age 10 to 15 years old, or 21 years and over.

6. **Vulnerable Subjects:** Will any vulnerable subjects be included? If so, identify the subject groups and justify their involvement.

Children will be included. The whole rationale for this study is that while much work has been done on adults, pollution is thought to primarily affect children. This study is being performed to understand and so combat the mechanisms involved.

UCLA students and staff will be included. In the past several members of the UCLA community have asked to participate in similar studies. While not actively recruiting this population we have no reason to exclude them as part of the general population pool.

7. **Method of Subject Identification and Recruitment:** What method(s) will be used to identify and recruit prospective subjects? Attach a copy of any planned advertisements/notices and letters to potential subjects.

Given the small number of subjects needed, subjects will be recruited by word of mouth. We receive numerous inquiries each week about ongoing studies so at the moment we do not believe we need to advertise. Informed consent is obtained from subjects by the Principal Investigator or co-PI by explaining the nature of the request for experimentation, the purpose of the research (in layman's terms) and the potential benefits and hazards. Detailed information is provided in the informed consent form, which is signed by the subject. In the case of children, the parent/guardian and the child are spoken to. It is made clear to the child that there is no obligation to do the study and that even if the parent agrees, they should not agree to do the study if they do not want to or feel uncomfortable. Both the consent and the assent form must be signed.

8. **Methods and Procedures Applied to Human Subjects:**

All the procedures described are being carried out solely for research purpose and thus are experimental. All these procedures have been previously approved by the UCLA for adults.

Nasal lavage: Nasal lavage is performed by having the subjects sit and close their nasopharynx whilst tilting their necks back 45° from the horizontal. Into each nostril 5 ml of normal saline that had been pre-warmed to 37° C is delivered by pipette. After 10 seconds, during which the subjects shake their heads softly from side to side, they bring their heads forward, expelling the wash fluid into a plastic receptacle. The fluid is then transferred to a separate tube. The subjects then perform up to four subsequent nasal washes at 30 second intervals with each wash being collected into a separate tube. Such lavages will be performed before and 24 hours after challenge with DEP or saline so as to examine the changes induced by the various challenges. Nasal challenge has been used in children as young as 2 years old. In previous studies we have observed that children between 10-15 years can perform this technique as ably as adults.

Diesel exhaust particle (DEP) nasal challenge: - A small amount of fluid (about 5 drops) containing diesel exhaust particles are be sprayed into the nose with an atomizer. The maximum amount of DEP used is 0.3 mg of particles by weight; this is equivalent to an average 2 day exposure to Los Angeles air and is less than that that would be encountered from passing behind a diesel bus as it starts up. The amount is therefore no more than that which the subject may be exposed to in a natural environment. The DEP used has been tested and is devoid of endotoxin.

Study design

A double-blind randomized cross-over exposure design will be used to test responses to four different DEP doses - 0 (control), 30, 100 or 300 µg. Subjects will perform nasal lavage sampling immediately before and 24 hrs after each DEP challenge. Subjects will be randomized to one of four groups which will receive one of the doses of DEP. Each subject will be assigned at random to one of the 24 possible sequences of 4 exposures. No two subjects will have the same sequence. After a four week washout period, subjects will return for one of the three alternative challenges. The subjects will return for the third and then the final challenge each after a four weeks hiatus. A 4-week washout period is chosen based on our previous DEP studies. We will use the cells recovered from the nasal lavages to measure expression of two key Phase II antioxidant genes (NQO1 and GSTM1).

- 9 **For Research Involving Survey, Questionnaires, etc.: N/A**

- 10 **FDA Approval: N/A**

11 Data Collection, Storage and Confidentiality:

- a) How will data be collected and recorded? Will it be associated with personal identifiers or coded to protect personal privacy?

Data will be recorded using a numerical code and recorded in a laboratory report book for the study. The numerical code will known only by the P.I. and the co-PI. All reference in published materials will use the code and no other details to ensure anonymity and confidentiality.

- b) Where will the data be stored during the study and how will it be secured?

The data will be stored in a locked cabinet or drawer in the Division of Clinical Immunology and Allergy. The key to the codes will be kept separately from the recorded data.

- c) Who will have access to the data and/or to the codes? If data with subject identifiers will be released, specify the person(s) or agency to whom this information will be released.

The P.I. and investigators will be the only individuals with access to the data and codes.

- d) What will happen to the data when the research has been completed

The data will be stored for 3 years in a locked space, and destroyed thereafter.

12 Potential Risks and Discomforts:

Nasal lavage: The risks of nasal lavage are that some salt water may be swallowed, although possibly unpleasant it is harmless.

Diesel exposure

Diesel is considered a toxic air contaminant in California, and a "likely" carcinogen by the U.S. EPA. However, it is clear that its potential effects on cancer come only upon high level life-time exposures and not acute exposures. Indeed, the US EPA itself has given approval for its own scientists to do human diesel exposures. It should be stressed that the concentrations used here mimic real world exposure levels. It is very important to realize that the cancer risk associated with diesel is solely for lung cancer. In this case following nasal challenge, the amount that will reach the lung is extremely small; most is cleared by the nasal cilia in 48 hours or else swallowed and naturally excreted. In rare cases, subjects may experience an unpleasant taste like soot. Some itching may occur.

13 Risk Classification: The risk classification is minimal**14 Minimizing Risks:**

Every effort has been made to minimize any potential risk. The subjects will always be visually monitored by the staff and a physician (Dr. Casillas) will be present, nearby, and/or reachable by beeper. The PI is a member of the Clean Air Scientific Advisory Committee for the US EPA and helped review the Health Assessment document for diesel. If any new information regarding risks becomes available, he will be one of the first to know.

15 Potential Benefits:

- a) The benefit to the subjects is the knowledge of how efficiently they produce natural chemical defenses (Phase II antioxidants) in response to a pollutant.

b) The benefits to society are an increased understanding of how natural antioxidants regulate pollution-induced allergic responses in children and adults. Once this is understood, then intervention strategies can be designed to protect this susceptible population.

16 **Therapeutic Alternatives:** N/A

17 **Risk/Benefit Ratio:** Since the risks are minimal while the potential benefits are great, the ratio is low.

18 **Payment for Participation:** Subjects will be reimbursed \$20/visit-session. Time for coming in, performing a nasal lavage, getting a DEP nasal challenge and then coming in next day for a follow-up lavage, the subject will receive \$40. Since there are 4 challenge conditions (DEP at 0, 30, 100 or 300 µg) and therefore a maximum of 8 visits, the maximum payment will be \$160. Please note that in the case of the children, all payments will be to the child and not to the parent/guardian. Additionally, we provide a \$7.00 parking validation for each day for a cost of up to \$56. In the case of children, this will be paid to the parent if they drove the student to UCLA and parked there.

19 **Financial Obligations of the Subjects:** There is no financial obligation towards the subject.

20 **Emergency Care and Compensation for Research-Related Injury:** N/A

21 **Capacity to Consent:** All adult subjects will have the capacity to give informed consent.

22 **Personnel Inviting Participants:** The Principal Investigator David Diaz-Sanchez, Ph.D. or the Co-PI Adrian Castillas, M.D. will be inviting subjects to participate.

23 **Process of Consent:** The consent process will take place in CHS, room 57-115. The consent form will be read by the subject, and then they will be asked to explain it back to the supervising researcher. The subject will be asked if they have any additional questions, and they will be told to sign it at their leisure. If necessary, subject has option to take some time and think about participation. In the case of children, the child must assent regardless of whether the parent/guardian does. The child will be reassured that they need not agree to the study even if their parent does and that nobody will be angry or upset if they decide not to go ahead. They will be told that they need not make any decision there and then, that they can go home and think about it.

24 **Comprehension of the Information Provided:** The Principal Investigator or co-PI will be determining if the subject understands the information provided. For the adults, they will ask the subject to explain what they understand: the procedure, risk/benefits, etc. For the children, they will ask the children simple questions regarding the study such as "How many times do you think you need to visit us?" or "what good things or bad things do you think may happen if you do the study?".

25 **Information Withheld From Subjects:** No information is to be withheld from the subject.

26 **Consent/Assent Forms:** The forms to be used will be adult consent forms which will also serve as parental consent forms and child assent forms.

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**Division of Clinical Immunology and Allergy
UCLA School of Medicine**

**CONSENT FOR PARTICIPATION IN RESEARCH: Pollution-enhanced allergic
inflammation & Phase II enzymes**

You are asked to participate in a research study conducted by Dr. David Diaz-Sanchez and Adrian Casillas from the Division of Clinical Immunology and Allergy at the University of California, Los Angeles. This study is sponsored by the National Institutes of Health (NIH) and the Environmental Protection Agency. You have been asked to participate in this study because you are a person who can make responses to pollutants. Your participation in this study is entirely voluntary. You should read the information below and ask questions about anything you do not understand before deciding whether or not to participate. The number of subjects at UCLA that are expected to enroll in this study is approximately 60. The duration of your participation if you complete all the study should last approximately twelve weeks.

Disclosure: Your health care provider may be an investigator of this research protocol, and as an investigator, is interested in both your clinical welfare and in the conduct of this study. Before entering this study or at any time during the research, you may ask for a second opinion about your care from another doctor who is in no way associated with this project. You are not under any obligation to participate in any research project offered by your physician.

PURPOSE OF THE STUDY

The purpose of this study is to compare the ability of adults and children in producing natural chemicals (antioxidants) that protect against pollution.

PROCEDURES

If you volunteer to participate in this study, you will be asked to do the following:

1) Nasal Challenge

The nasal challenge, involves placing several small mists of fluid into the nasal cavity. Each challenge will consist of between one and five small samples (0.1cc, or about three drops) of fluid applied to the nasal cavity through a sprayer and will contain soot from a diesel truck (diesel exhaust particles).

The diesel exhaust particles will be administered in small mists of fluid containing different amounts of particles. The highest amount of particles you may be given is equal to two day's average urban exposure in Los Angeles. This is less than you would receive from passing behind a diesel bus as it starts its engine. There have been no reported adverse reactions to this procedure, other than the possible uncomfortable feeling of fluid being sprayed into your nose.

2) Nasal Lavage. Samples of nasal lavage fluid will be obtained which involves tilting the head back, holding your breath for a short period of time, having one teaspoon of sterile salt water placed in one nostril, and then recovering the fluid by repositioning your head down and catching the fluid as it exits your nose.

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3. Overall. On day 1, you will do a nasal lavage and then be challenged with diesel exhaust particles. Next day you will do another nasal lavage. You will perform the same schedule after a period of four weeks, eight weeks or 12 weeks. Each time you will be challenged with a different amount of diesel exhaust particles.

POTENTIAL RISKS AND DISCOMFORTS

During the nasal lavage, there is a possibility of swallowing this fluid which has a salt water taste but contains no other substances. Additional potential complications of nasal lavage include aspiration (inhalation) of the fluid which is uncomfortable, but the amount of fluid is so small that there is no known possibility of any respiratory complication.

Diesel exhaust particles contain "polycyclic aromatic hydrocarbons" which are known cancer-causing agents (called carcinogens) in laboratory animals and man when repeatedly exposed in high enough concentrations over years. Men regularly exposed to diesel exhaust at work for many years have shown slightly higher rates of cancer than similar men in "clean" jobs. For these reasons the State of California has classified diesel exhaust as a carcinogen. The excess cancer risk from one or a few diesel exposures like the one used on this study, if any, is very small. Certainly no more than the risk from spending a few days in a city like Los Angeles. You may experience some irritation (itchiness) in your nose for a few moments.

ANTICIPATED BENEFITS TO SUBJECTS

This study is not being done to improve your condition or health. You have the right to refuse to participate in this study. Your only benefit is that you may learn how well your body makes antioxidants in response to pollutants

ANTICIPATED BENEFITS TO SOCIETY

This study may benefit society by increasing our understanding of the mechanisms that induce allergic disease, and why children are more susceptible to pollution effects than adults..

ALTERNATIVES TO PARTICIPATION

The alternative to participation is not to participate.

PAYMENT FOR PARTICIPATION

You will be paid \$20.00 per lab visit (total of 8 visits). This amount will be paid whether you complete the session or withdraw for any reason. After your participation you will not be required to return for a follow-up visit. The total payment for this study is \$160. Parking will also be reimbursed (\$7/visit) if applicable.

POSSIBLE COMMERCIAL PRODUCTS

All tissue and/or fluid samples are important to this research study. Your sample will be owned by the University of California or by a third party designated by the University (such as another university or a private company). If a commercial product is developed from this research project, the commercial product will be owned by the

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University of California or its designee. You will not profit financially from such a product.

INFORMATION ABOUT YOUR SAMPLE

On the checklist below, you are asked to let us know if you would like to receive information about the results of this study. There are two types of information you may receive:

1. general information about what this study found (or conclusions of the study)
2. specific information about what the study found about your individual sample.

You may also choose not to receive any information. Research is a long and complicated process. Obtaining general information from a project may take years. Even if there is general information from a project, there may not be personal information for every participant.

FINANCIAL OBLIGATION

Neither you nor your insurance company will be billed for your participation in this research.

EMERGENCY CARE AND COMPENSATION FOR INJURY

If you are injured as a direct result of research procedures not done primarily for your own benefit, you will receive treatment at no cost. The University of California does not provide any other form of compensation for injury.

PRIVACY AND CONFIDENTIALITY

The only people who will know that you are a research subject are members of the research team and, if appropriate your physicians and nurses. No information about you, or provided by you during the research, will be disclosed to others without your written permission, except:

- if necessary to protect your rights or welfare (for example, if you are injured and need emergency care); or
- if required by law.

When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity.

Authorized representatives of the National Institute of Allergy and Infectious Disease (NIAID) and the Public Health Service (PHS) may need to review records of individual subjects. As a result, they may see your name; but they are bound by rules of confidentiality not to reveal your identity to others.

Your samples will be kept private and a code will be assigned to them, known only by the investigators.

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PARTICIPATION AND WITHDRAWAL.

Your participation in this research is **VOLUNTARY**. If you choose not to participate, that will not affect your relationship with UCLA (or UCLA Medical Center), or your right to health care or other services to which you are otherwise entitled. If you decide to participate, you are free to withdraw your consent and discontinue participation at any time without prejudice to your future care at UCLA.

WITHDRAWAL OF PARTICIPATION BY THE INVESTIGATOR

The investigator may withdraw you from participating in this research if circumstances arise which warrant doing so. If you become ill during the research, you may have to drop out, even if you would like to continue. The investigator, Dr. Andrew Saxon, will make the decision and let you know if it is possible for you to continue. The decision may be made either to protect your health and safety, or because it is part of research plan that people who develop certain conditions may not continue to participate.

If you must drop out because the investigator asks you to (rather than because you have decided on your own to withdraw), you will be paid the appropriate amount for completed procedures.

NEW FINDINGS

During the course of the study, you will be informed of any significant new findings (either good or bad), such as changes in the risks or benefits resulting from participation in the research or new alternative to participation, that might cause you to change your mind about continuing in the study. If new information is provided to you, your consent to continue participating in this study will be re-obtained.

IDENTIFICATION OF INVESTIGATORS

In the event of a research related injury or if you experience an adverse reaction, please immediately contact one of the investigators listed below. If you have any questions about the research, please feel free to contact David Diaz-Sanchez, Ph.D., at 310-825-9261; 10833 Le Conte Avenue, Room 52-175, Center for Health Sciences, UCLA, Los Angeles, CA 90095-1680. Dr. Diaz-Sanchez can be reached 24 hours a day/7days a week by calling 310 709 1459. Additionally, you can reach the co-PI, Dr. Adrian Casillas at 310 825 1153.

RIGHTS OF RESEARCH SUBJECTS

You may withdraw your consent at any time and discontinue participation without penalty. You are not waiving any legal claims, rights or remedies because of your participation in this research study. If you have questions regarding your rights as a research subject, you may contact the Office for Protection of Research Subjects, 2107 Ueberroth Building, UCLA, Box 951694, Los Angeles, CA 90095-1694, (310) 825-8714.

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SIGNATURE OF RESEARCH SUBJECT OR LEGAL REPRESENTATIVE

I have read (or someone has read to me) the information provided above. I have been given an opportunity to ask questions and all of my questions have been answered to my satisfaction. I have been given a copy of this form, as well as a copy of the Subject's Bill of Rights.

BY SIGNING THIS FORM, I WILLINGLY AGREE TO PARTICIPATE IN THE RESEARCH IT DESCRIBES.

Name of Subject

Signature of Subject

Date

Name of Parent or Legal Guardian (if applicable)

Signature of Parent or Legal Guardian

Date

INFORMATION ABOUT MY SAMPLE

Please indicate by checking and initialing the category below what type of information you want to receive. It is your responsibility to let the investigator know if your address and/or telephone number changes. The contact information is in this informed consent form under "Identification of Investigators."

- ☐ _____ General Information about what the study found
- ☐ _____ Specific Information about what the study found about my sample
- ☐ _____ I do not want any information about my sample

SIGNATURE OF INVESTIGATOR

I have explained the research to the subject and answered all of his/her questions. I believe that he/she understands the information described in this document and freely consents to participate.

Name of Investigator

Signature of Investigator

Date (must be the same as subject's)

DATE OF PREPARATION: 05-05-04

UCLA IRB #:

EXPIRATION DATE:

DEPARTMENT OF MEDICINE
Division of Clinical Immunology and Allergy
UCLA School of Medicine

ASSENT TO PARTICIPATE IN RESEARCH

Pollution-enhanced allergic inflammation & Phase II enzymes

1. My name is David Diaz-Sanchez.
2. We are asking you to take part in a research study because we are trying to learn more about pollution and why it causes children to be more likely to have hay fever. Hay fever is when you sneeze and have a runny nose when you are near certain weeds or plants.
3. If you agree to be in this study:
 - a) We will ask you to put a small amount of salty water in your nose. You will keep it there for 5 seconds and then blow it into a cup.
 - b) We will spray the inside of your nose with salty water or salty water mixed with some diesel soot. This may cause you to have a runny or itchy nose for a few minutes.
 - c) The next day we will ask you to come back and we will again put a small amount of salty water in your nose. You will keep it there for 5 seconds and then blow it into a cup.
 - d) We will ask you to come back 3 other times to repeat the experiment.
 - e) The number of visits you will make may be as few as one or as many as 8.
4. Some of the following things could happen to you from being in this study:
 - a) Your eyes and throat may become itchy and you may get a headache. Breathing diesel soot over a long time is bad for you and may cause illness. However, you will only receive a small bit during this study, less than what you would get if you passed behind a bus.
 - b) You may swallow some salty water when we place it in your nose.
 - c) You may sneeze and have a runny or stuffy nose when we spray your nose.
5. There is no direct benefit from you performing this study except for learning how well your body can cope with pollution.
6. Please talk this over with your parents before you decide whether or not to participate. We will also ask your parents to give their permission for you to take part in this study. But even if your parents say "yes" you can still decide not to do this.

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- If you don't want to be in this study, you don't have to participate. Remember, being in this study is up to you and no one will be upset if you don't want to participate or even if you change your mind later and want to stop.
8. You can ask any questions that you have about the study. If you have a question later that you didn't think of now, you can call me at (310) 825 9261 or ask me next time. If you have hay fever, you may call me at any time to ask questions about your hay fever.
 9. Signing your name at the bottom means that you agree to be in this study. But remember you can change your mind at any time. You and your parents will be given a copy of this form after you have signed it.

Name of Subject

Date

Date of preparation: 08/08/04

U-1 HSPC Number:

E. .ation Date:

HS-1(a) HIPAA Research Application**UCLA IRB*****Pollution-enhanced allergic inflammation & Phase II enzymes*****P.I. David Diaz-Sanchez****I. Identify the Information that will be collected**

- A. We will not review, collect information from or put information into MEDICAL RECORDS.
- B. We will obtain nasal lavage as specimens from the research subjects. The only data attached to the specimens will be a code. This code will be available only to the PI and co-PI and will be used to identify the subjects name, address, date of birth and telephone number.

II

- A. We will obtain the HIPAA authorization of the subjects.